PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Johannes Henricus Matthias SCHELLENS, et al.

Appln. No.: PCT/NL00/00331 Group Art Unit: Not Yet Assigned

Confirmation No.: Not Yet Asssigned Examiner: Not Yet Assigned

Filed: November 19, 2001

For: A METHOD OF IMPROVING BIOAVAILABILITY OF ORALLY ADMINISTERED DRUGS, A METHOD OF SCREENING FOR ENHANCERS OF SUCH BIOAVAILABILITY AND NOVEL PHARMACEUTICAL COMPOSITIONS FOR ORAL DELIVERY OF DRUGS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Amend the specification by inserting before the first line the sentence:

CROSS REFERENCE TO RELATED APPLICATION

This is a Continuation-in-Part of International Application PCT/NL00/00331, with an international filing date of May 17, 2000, which was published under PCT Article 21(2) in English, and the complete disclosure of which is incorporated into this application by reference.

IN THE CLAIMS:

Please enter the following amended claims:

3. Method according to claim 1, wherein the cells are normal cells.
4. Method according to claim 1, wherein the inhibitor is a selective inhibitor of BCRP.

5. Method according to claim 1, wherein the inhibitor is selected from acridine derivatives, quinoline derivatives, isoquinoline derivatives and combinations thereof.
6. Method according to claim 1, wherein the inhibitor is GF120918, XR 9051 or XR 9576.
7. Method according to claim 1, wherein the bioenhancer is a mycotoxin.
9. Method according to claim 1, wherein the bioenhancer has a higher affinity for BCRP than for P-gp.
10. Method according to claim 1, wherein the bioenhancer has a higher affinity for BCRP than for MRP.
11. Method according to claim 1, wherein the bioenhancer inhibits binding of ATP to a BCRP mediated and/or related drug transport protein.
13. Method according to claim 1, wherein the pharmaceutically active compound is selected from the group consisting of indolizino-quinoline derivatives, camptothecin derivatives, anthraquinone derivatives and quinazoline derivatives.
23. Use of a pharmaceutically active compound in combination with a bioenhancer as defined in claim 1 as active ingredients in the preparation of a pharmaceutical composition for oral delivery of the pharmaceutically active compound, said pharmaceutical composition providing an increased systemic exposure of cells selected from tumor cells and normal cells to said pharmaceutically active compound in comparison to a corresponding pharmaceutical composition in which said bioenhancer is absent.
24. Use of a pharmaceutically active compound in combination with a bioenhancer as defined in claim 1 as active ingredients in the preparation of a pharmaceutical composition for oral delivery of the pharmaceutically active compound, said pharmaceutical composition providing an increased reversal of drug resistance in human and animal disorders related to overexpression of BCRP.
27. Use of a compound selected according to claim 26 as bioenhancer in a pharmaceutical composition.

REMARKS

Entry and consideration of this Amendment is respectfully requested.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

3. Method according to claim 1 ~~or claim 2~~, wherein the cells are normal cells.
4. Method according to claim 1 ~~any of the preceding claims~~, wherein the inhibitor is a selective inhibitor of BCRP.
5. Method according to claim 1 ~~any of the preceding claims~~, wherein the inhibitor is selected from acridine derivatives, quinoline derivatives, isoquinoline derivatives and combinations thereof.
6. Method according to claim 1 ~~any of the preceding claims~~, wherein the inhibitor is GF120918, XR 9051 or XR 9576.
7. Method according to claim 1 ~~any of the preceding claims~~, wherein the bioenhancer is a mycotoxin.
9. Method according to claim 1 ~~any of the preceding claims~~, wherein the bioenhancer has a higher affinity for BCRP than for P-gp.
10. Method according to claim 1 ~~any of the preceding claims~~, wherein the bioenhancer has a higher affinity for BCRP than for MRP.
11. Method according to claim 1 ~~any one of the preceding claims~~, wherein the bioenhancer inhibits binding of ATP to a BCRP mediated and/or related drug transport protein.
13. Method according to claim 1 ~~any of the preceding claims~~, wherein the pharmaceutically active compound is selected from the group consisting of indolizino-quinoline derivatives, camptothecin derivatives, anthraquinone derivatives and quinazoline derivatives.
23. Use of a pharmaceutically active compound in combination with a bioenhancer as defined in claim 1 ~~any of the preceding claims~~ as active ingredients in the preparation of a pharmaceutical composition for oral delivery of the pharmaceutically active compound, said

pharmaceutical composition providing an increased systemic exposure of cells selected from tumor cells and normal cells to said pharmaceutically active compound in comparison to a corresponding pharmaceutical composition in which said bioenhancer is absent.

24. Use of a pharmaceutically active compound in combination with a bioenhancer as defined in claim 1~~any of the preceding claims~~ as active ingredients in the preparation of a pharmaceutical composition for oral delivery of the pharmaceutically active compound, said pharmaceutical composition providing an increased reversal of drug resistance in human and animal disorders related to overexpression of BCRP.

27. Use of a compound selected according to claim 26 as bioenhancer in a pharmaceutical composition~~ according to claim 22~~.